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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,382	04/09/2004	Guoqing P. Chen		1603

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Advenchen Laboratories LLC/ Paul Chen
9135 Reseda BLVD.
Suite 238
Northridge, CA 91324

EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/821,382

Applicant(s)

CHEN, GUOQING P.

Examiner

Deepak Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-10 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

Claims 1 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Kim et al., WO 04/099186 (International Filing Date May 26, 2003). The instant claims read on reference disclosed compounds, see the compounds of formula (1) in page 3; the corresponding species in page 9 (the last structural formula under Reaction Scheme 1) and the compounds of Example 4.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant relies on the amendment to the claims wherein it is recited that "R₄ is lower alkylamino heterocyclyl with the proviso that lower alkylamino defined herein is not para-substituted with -CH₂NH- when Z is the phenyl ring". This is not deemed to be persuasive because the recitation is not clear. It is recited that 'lower alkylamino is not para-substituted with -CH₂NH-' which is confusing because the term "lower alkylamino" itself represents an alkyl group (e.g., -CH₂-) attached to an amino (e.g., -NH-) and therefore, represents the -CH₂NH-. The recitation that 'lower alkylamino is not further substituted with -CH₂NH-' appears to be repetitive or redundant. The reference compounds have a -CH₂-NH-(4-methyl-

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piperazin-1-yl) group attached to the phenyl at the para-position. The instant proviso lacks clarity and is not seen to effectively exclude the reference compound.

The following rejections are necessitated by the amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim has been amended to include the following recitations in the definition of R₄:

aminoheterocyclyl with the proviso that heterocyclyl defined herein is not selected from N-lower alkylpyrrolidinyl or N-lower alkylpiperidinyl,

lower alkylamino heterocyclyl with the proviso that lower alkylamino defined herein is not para-substituted with -CH₂NH- when Z is the phenyl ring,

which lacks description in the specification as filed. MPEP § 2173.05(i) states that “Any negative limitation or exclusionary proviso must have basis in the original disclosure”. See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff’d mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a

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negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In the instant case, applicant has not provided wherein the original disclosure the recitation “aminoheterocyclyl with the proviso that heterocyclyl defined herein is not selected from N-lower alkylpyrrolidiyl or N-lower alkylpiperidinyll” is supported. Further, regarding the second proviso - the new concept that has been introduced by the instant recitation “R₄ is lower alkylamino heterocyclyl with the proviso that lower alkylamino defined herein is not para-substituted with -CH₂NH- when Z is the phenyl ring”, is the specific relationship between R₄ and Z. As per the recitation, the definition of R₄ depends on definition of Z. This specific relationship of connectivity was previously not disclosed. This notion that the definition of one variable depends on the definitions of other variable is new. The definition of a variable is no longer independent.

2. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a composition comprising a **solvate** or **hydrate** of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factual Basis:

1. Specification has no working example of **solvate** of compound of formula (I); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have

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not formed solvate as evident from spectral data provided for these compounds.

2. Searching the pertinent art in the related pyrimidine area did not result in support for such solvates of instant pyrimidine compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant *Wands* factors. Hence, the burden of establishing the *prime facie* case is met with.

Scope of enablement rejection:

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate or hydrate thereof. Specification is not adequately enabled as to how to make solvate of compounds of Formula I. Specification has no example of solvate of the instant compounds and there is no enabling disclosure of such solvates.

The compound of formula (I) embrace substituted pyrimidine compounds substituted with variable groups R^1 , R^2 , etc. Careful calculation of the number of compounds embraced in the instant formula I results in a large number of compounds. The term "substituted" embraces

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undefined number of variable groups and thus, the genus embraced by the claims is excessively large and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates is unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

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Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that “Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph”.

2. The predictability or lack thereof in the art:

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvate of instant compound. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

4. The presence or absence of working examples:

Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents,

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temperatures and other parameters. The experimentation is potentially open-ended. The specification does not provide any working example of a solvate of the compound of formula (I).

The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

5. The breadth of the claims & the quantity of experimentation needed:

Specification provides no support, as noted above, for compounds generically embraced by the claims would lead to desired solvate of the compound of formula (I). As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula (I) embraced in the instant claims in view of the pertinent reference teachings.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims, in the definition of R₄, the following recitation “with the proviso that lower alkylamino defined herein is not para-substituted with –CH₂NH- when Z is the phenyl ring” is confusing and not clear. The term “lower alkylamino” itself represents an alkyl group (e.g., –CH₂-) attached to an amino (e.g., –NH-) and therefore, represents the –CH₂NH-. The recitation that ‘lower alkylamino is not further substituted with –CH₂NH-’ appears to be repetitive or redundant.
2. Claim 10 recites the limitation "compound of formula (I) ... or a hydrate or solvate thereof" in lines 3-4. There is insufficient antecedent basis for this limitation in claims 1-8 on which claim 10 is dependent. Claims 1-8 do not recite the terms “hydrate” or “solvate” in the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

December 7, 2006